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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,390	02/01/2002	Hal S. Padgett	P-LG 4878	4639

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,390	PADGETT ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The restriction requirement is withdrawn because it is in error. Specifically, there is a preliminary amendment, filed July 30, 2002, which was inadvertently overlooked which cancelled claims 1-65 and added new claims 66-86. These new claims would all fall within a single restriction group, and would in fact be within the elected restriction group. Since the restriction was made on cancelled claims, it is moot and erroneous. This action will address all of the currently pending claims 66-86.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 67, 69-74, 78, 79 and 83-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Birkenkamp et al (DNA Research (1995) 2:9-14).

Birkenkamp teaches an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs (see figure 1, panels B-D) comprising:

a) preparing at least one heteroduplex polynucleotide (see figure 1),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see page 12 and page 13,

figure 3, where T4 DNA polymerase is used) and an agent with strand cleavage activity (see page 12 and page 13, figure 3, where endonuclease VII is used),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see page 13, figure 3, where the enzymes correct the heteroduplex).

With regard to claim 69, Birkenkamp teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see page 13, figure 3).

With regard to claims 70-72, Birkenkamp teaches the addition of T4 DNA ligase (see page 13, figure 3).

With regard to claims 73-74, Birkenkamp teaches the use of T4 endonuclease VII (see page 13, figure 3).

With regard to claims 78-79, Birkenkamp teaches the use of T4 DNA polymerase (see page 13, figure 3).

With regard to claim 83, Birkenkamp teaches the use of T4 Endonuclease VII, T4 DNA polymerase and T4 DNA ligase (see page 13, figure 3).

With regard to claims 84-86, Birkenkamp teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see page 13, figure 3 and page 13, columns 1 and 2, especially with regard to diversity increased in panel 8, relative to panel 3).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Birkenkamp et al (DNA Research (1995) 2:9-14) as applied to claims 67, 69-74, 78, 79 and 83-86 above.

Birkenkamp teaches an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs (see figure 1, panels B-D) comprising:

a) preparing at least one heteroduplex polynucleotide (see figure 1),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see page 12 and page 13, figure 3, where T4 DNA polymerase is used) and an agent with strand cleavage activity (see page 12 and page 13, figure 3, where endonuclease VII is used),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see page 13, figure 3, where the enzymes correct the heteroduplex).

With regard to claim 69, Birkenkamp teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see page 13, figure 3).

With regard to claims 70-72, Birkenkamp teaches the addition of T4 DNA ligase (see page 13, figure 3).

With regard to claims 73-74, Birkenkamp teaches the use of T4 endonuclease VII (see page 13, figure 3).

With regard to claims 78-79, Birkenkamp teaches the use of T4 DNA polymerase (see page 13, figure 3).

With regard to claim 83, Birkenkamp teaches the use of T4 Endonuclease VII, T4 DNA polymerase and T4 DNA ligase (see page 13, figure 3).

With regard to claims 84-86, Birkenkamp teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see page 13, figure 3 and page 13, columns 1 and 2, especially with regard to diversity increased in panel 8, relative to panel 3).

Birkenkamp does not teach adding the ingredients in the particular order claimed in claim 68.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any order of adding ingredients, as MPEP 2144.04 IV.C notes "Selection of any order of mixing ingredients is prima facie obvious." Here, there is no particular reason why the order is shown to have any effect on the reaction other than to add the first necessary reactant first, the second second and the third reactant needed is added last. So in the absence of any evidence of unexpected results with regard to the order of addition, the claimed order is prima facie obvious as noted by the MPEP section above.

7. Claims 75-77 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birkenkamp et al (DNA Research (1995) 2:9-14) as applied to claims 67, 69-74, 78, 79 and 83-86 above in view of Arnold et al (WO 99/29902).

Birkenkamp teaches an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs (see figure 1, panels B-D) comprising:

a) preparing at least one heteroduplex polynucleotide (see figure 1),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see page 12 and page 13, figure 3, where T4 DNA polymerase is used) and an agent with strand cleavage activity (see page 12 and page 13, figure 3, where endonuclease VII is used),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see page 13, figure 3, where the enzymes correct the heteroduplex).

With regard to claim 69, Birkenkamp teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see page 13, figure 3).

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With regard to claims 78-79, Birkenkamp teaches the use of T4 DNA polymerase (see page 13, figure 3).

With regard to claim 83, Birkenkamp teaches the use of T4 Endonuclease VII, T4 DNA polymerase and T4 DNA ligase (see page 13, figure 3).

With regard to claims 84-86, Birkenkamp teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see page 13, figure 3 and page 13, columns 1 and 2, especially with regard to diversity increased in panel 8, relative to panel 3).

Birkenkamp does inherently teaches the application of the method to creating populations of homoduplexes starting with heteroduplexes but does not focus on a screening method to create the homoduplexes. Birkenkamp does not teach the use of CEL-1 or other cleavage agents.

Arnold teaches the application of mismatch correction methods such as those of Birkenkamp to evolving polynucleotides by performing the steps in claim 66 to heteroduplex parental nucleic acids which are corrected to form a heterogenous population of homoduplex nucleic acids (see page 12, paragraph 3, for example). Arnold expressly teaches the use of in vitro DNA repair systems such as those of Birkenkamp (see page 17, line 30 to page 18, line 4).

With regard to claims 75-77, Arnold teaches mutagens such as chemicals like hydroxylamine (see page 10, line 30), intercalating agents (see page 10, line 33 to page 11, line 1) and ionizing radiation (see page 11, lines 1-3).

With regard to claim 80, Arnold teaches the use of E. coli extracts for repair, which will include E. coli Pol 1 (se page 17, line 33).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the in vitro mismatch repair method of Birkenkamp in the evolution method of Arnold since Arnold expressly teaches that the heteroduplex correction method may be performed in vitro and Birkenkamp provides the enzymes and techniques necessary to perform the heteroduplex correction, so Birkenkamp provides a solution to the method proposed by Arnold. It would further have been prima facie obvious to use the mutagens taught by Arnold since Arnold teaches that these are known equivalents. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are

functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

8. Claims 66 and 81-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birkenkamp et al (DNA Research (1995) 2:9-14) as applied to claims 67, 69-74, 78, 79 and 83-86 above in view of Arnold et al (WO 99/29902) and further in view of Oleykowski et al (Nucleic Acids Research (1998) 26(20):4597-4602).

Birkenkamp teaches an in vitro method (see figure 2) of making linear sequence variants (see figure 1, where hairpins are linear), from at least one heteroduplex polynucleotide wherein said heteroduplex has at least two noncomplementary nucleotide base pairs (see figure 1, panels B-D) comprising:

a) preparing at least one heteroduplex polynucleotide (see figure 1),

b) combining said heteroduplex polynucleotide with an effective amount of an agent with both exonuclease activity and polymerase activity (see page 12 and page 13, figure 3, where T4 DNA polymerase is used) and an agent with strand cleavage activity (see page 12 and page 13, figure 3, where endonuclease VII is used),

c) and allowing sufficient time for the percentage of complementarity to increase wherein at least one variant is made (see page 13, figure 3, where the enzymes correct the heteroduplex).

With regard to claim 69, Birkenkamp teaches concurrent addition of the exonuclease, polymerase and strand cleavage enzymes (see page 13, figure 3).

With regard to claims 70-72, Birkenkamp teaches the addition of T4 DNA ligase (see page 13, figure 3).

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With regard to claims 78-79, Birkenkamp teaches the use of T4 DNA polymerase (see page 13, figure 3).

With regard to claim 83, Birkenkamp teaches the use of T4 Endonuclease VII, T4 DNA polymerase and T4 DNA ligase (see page 13, figure 3).

With regard to claims 84-86, Birkenkamp teaches that the complementarity increases, resulting in homoduplex polynucleotides and an increase in diversity of the population (see page 13, figure 3 and page 13, columns 1 and 2, especially with regard to diversity increased in panel 8, relative to panel 3).

Birkenkamp does inherently teaches the application of the method to creating populations of homoduplexes starting with heteroduplexes but does not focus on a screening method to create the homoduplexes. Birkenkamp does not teach the use of CEL-1 or other cleavage agents.

Arnold teaches the application of mismatch correction methods such as those of Birkenkamp to evolving polynucleotides by performing the steps in claim 66 to heteroduplex parental nucleic acids which are corrected to form a heterogenous population of homoduplex nucleic acids (see page 12, paragraph 3, for example). Arnold expressly teaches the use of in vitro DNA repair systems such as those of Birkenkamp (see page 17, line 30 to page 18, line 4).

Birkenkamp in view of Arnold do not teach the use of Cel I.

Oleykowski teaches that Cel I is a superior substitute for T4 Endonuclease VII (see page 4602, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Cel 1 of Oleykowski in the in vitro mismatch repair method of Birkenkamp in view of Arnold since Oleykowski states,

"The principle of mismatch recognition by CEL 1 appears to be different from T4 endonuclease VII, which has also been used for
enzyme mutation detection. The latter is a resolvase which nicks one stand at the site of a mismatch and then in the other strand across from the DNA nick. Therefore, any nick can produce two corresponding fragments of the two colors. In the case of CEL 1, the two fragments of the two colors represent
two totally independent mutation detection events that complement each other to confirm the presence of the mutation. (See page 4602, column 1)."

Oleykowski further notes

"Other strengths of the CEL I mutation detection assay are its simplicity and its lack of preference for unique non-rnismatch DNA sequences. Background non-specific DNA nicking is very low. The high signal-to-noise ratio of CEL I using fluorescent dye-labeled PCR products often allows mutations to be detected by visual inspection of the GeneScan gel image. CEL I is a very stable enzyme, during both its purification, storage and assay (see page 4602, columns 1 and 2)."

So, an ordinary practitioner would have two separate motivations to substitute CEL 1 for T4 Endonuclease VII as used by Birkenkamp. First, CEL 1 operates differently than T4 endonuclease VII and only nicks one strand to result in truly indpendent mutation event detection. Second, CEL I mutation detection is simple, with low background nicking, high signal to noise ratio and uses a stable enzyme, which minimizes wasted effort in assays where the enzyme fails to function.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1634